



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 130805

TO: Michael Meller
Location: REM/3C03/3C18
Art Unit: 1654
Thursday, August 26, 2004

Case Serial Number: 09/077712

From: Deirdre Arnold
Location: Biotech-Chem Library
REM 1A64
Phone: 571-272-2532

Deirdre.Arnold@uspto.gov

Search Notes

Thank you for using STIC services.

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STIC SEARCH RESULTS FEEDBACK FORM

Biotech-Chem Library

Questions about the scope or the results of the search? Contact *the searcher or contact*

Mary Hale, Information Branch Supervisor
571-272-2507 Remsen E01 D86

Voluntary Results Feedback Form

➤ I am an examiner in Workgroup: Example: 1610

➤ Relevant prior art **found**, search results used as follows:

- ☐ 102 rejection
- ☐ 103 rejection
- ☐ Cited as being of interest.
- ☐ Helped examiner better understand the invention.
- ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature
(journal articles, conference proceedings, new product announcements etc.)

➤ Relevant prior art **not found**:

- ☐ Results verified the lack of relevant prior art (helped determine patentability).
- ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

Drop off or send completed forms to STIC/Biotech-Chem Library Remsen B



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=> fil lreg

FILE 'LREGISTRY' ENTERED AT 12:43:45 ON 26 AUG 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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LREGISTRY IS A STATIC LEARNING FILE

=> fil reg

FILE 'REGISTRY' ENTERED AT 12:43:48 ON 26 AUG 2004
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES: 25 AUG 2004 HIGHEST RN 732955-11-2
DICTIONARY FILE UPDATES: 25 AUG 2004 HIGHEST RN 732955-11-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> fil beilst

FILE 'BEILSTEIN' ENTERED AT 12:43:54 ON 26 AUG 2004
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FILE RELOADED ON OCTOBER 20, 2002
FILE LAST UPDATED ON JUNE 15, 2004

FILE COVERS 1771 TO 2003.
*** FILE CONTAINS 8,997,153 SUBSTANCES ***

>>>PLEASE NOTE: Reaction Data and substance data are stored in
separate documents and can not be searched together in one query.
Reaction data for BEILSTEIN compounds may be displayed
immediately with the display codes PRE (preparations) and REA
(reactions). A substance answer set retrieved after the search
for a chemical name, a compounds with available reaction
information by combining with PRE/FA, REA/FA or more generally
with RX/FA. The BEILSTEIN Registry Number (BRN) is the link
between a BEILSTEIN compound and belonging reactions. For mo
detailed reaction searches BRNs can be searched as reaction
partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

 * PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. *
 * SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE *
 * ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
 * ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
 * FOR PRICE INFORMATION SEE HELP COST *

NEW

* PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE
 SEARCHED, SELECTED AND TRANSFERRED.
 * NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES,
 ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A
 COMPOUND AT A GLANCE.

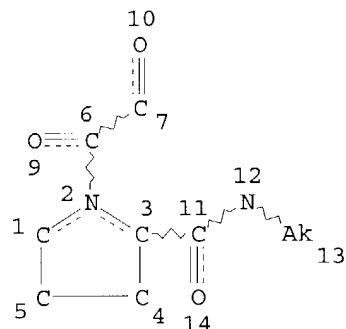
=> FIL STNGUIDE

FILE 'STNGUIDE' ENTERED AT 12:43:57 ON 26 AUG 2004
 USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
 COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
 AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
 LAST RELOADED: Aug 20, 2004 (20040820/UP).

=> d que 145

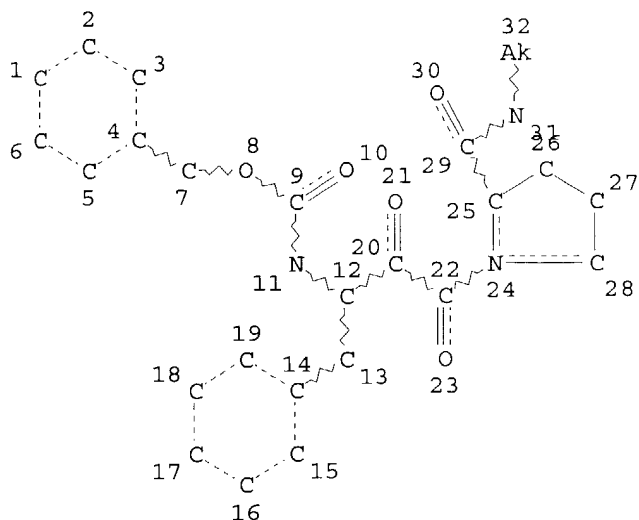
L23 STR



NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 13

STEREO ATTRIBUTES: NONE
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 L31 STR

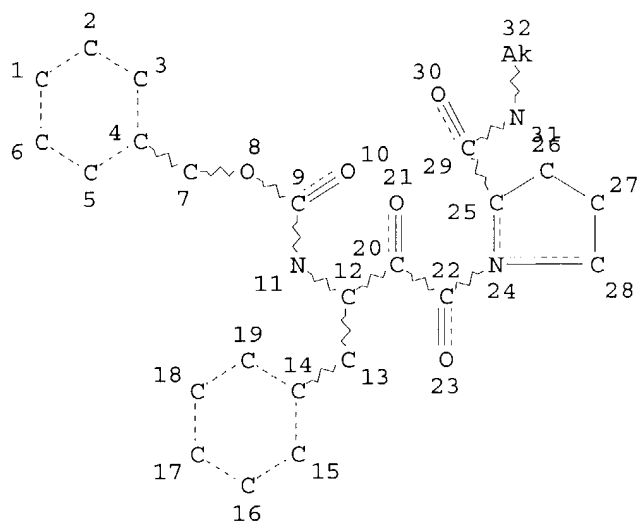


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GRAPH ATTRIBUTES:
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 NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE

L33 45 SEA FILE=REGISTRY SUB=L24 SSS FUL L31
 L35 41 SEA FILE=REGISTRY ABB=ON PLU=ON L33 NOT SEQUENCE/FS
 L37 STR



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 CONNECT IS E2 RC AT 27
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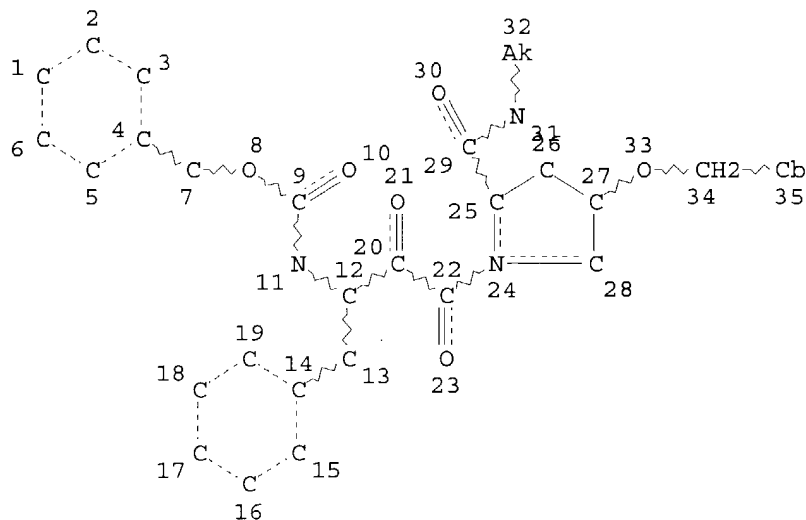
DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE

L40 5 SEA FILE=REGISTRY SUB=L35 SSS FUL L37
L41 36 SEA FILE=REGISTRY ABB=ON PLU=ON L35 NOT L40
L42 STR



NODE ATTRIBUTES:

CONNECT IS E1 RC AT 35
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 35
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E6 C AT 35

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE

L44 9 SEA FILE=REGISTRY SUB=L41 SSS FUL L42
L45 27 SEA FILE=REGISTRY ABB=ON PLU=ON L41 NOT L44

=> d 148

L48 ANALYZE L45 1- LC : 2 TERMS

TERM #	# OCC	# DOC	% DOC	LC
1	27	27	100.00	CA
2	27	27	100.00	CAPLUS

***** END OF L48***

=> d que nos 147

L23 STR
L24 206 SEA FILE=REGISTRY SSS FUL L23

*Files
containing
these CAS
RN's*

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L37          STR
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L42          STR
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L45          27 SEA FILE=REGISTRY ABB=ON  PLU=ON  L41 NOT L44
L47          3  SEA FILE=HCAPLUS ABB=ON  PLU=ON  L45

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=> d iall hitstr l47

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L47 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:801933 HCAPLUS

DOCUMENT NUMBER: 137:226

ENTRY DATE: Entered STN: 05 Nov 2001

TITLE: : of HIV protease and their

AUTHOR(S): *Date: 2001* Garret; Goodsell, David; Wong,

CORPORATE SOURCE: ., Kobe Gakuin Univ., 518
ishi-ku, Kobe, 651-2180, Japan

SOURCE: tware (2001), 7(3), 103-114
18-0761

PUBLISHER:

DOCUMENT TYPE:

LANGUAGE: English

CLASSIFICATION: 1-5 (Pharmacology)

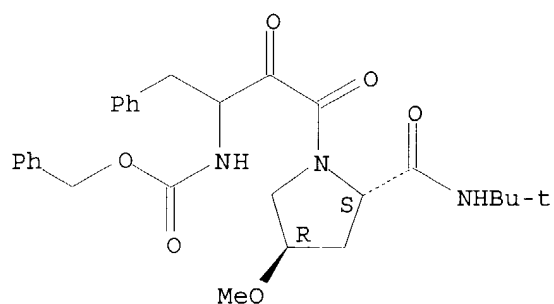
ABSTRACT:

The capability to propose feasible ways of binding a putative ligand inhibitor to a known receptor site is crucial to the successful structure-based drug design. A computer docking approach is to position or "dock" ligand and receptor mols. together in many different ways and then score each orientation by applying a reasonable evaluation function. AutoDock3.0 is an unbiased type docking program in which a user does not have to direct a ligand to an active site, but the system finds an optimal position after a ligand is placed in a random manner. Synthesized derivs. of the intact inhibitor (inh1) of HIV protease were investigated for their docking modes as compared with their Ki values. Among the derivs., inh3trans and inh6H were found to be more powerful inhibitors of HIV protease than the others. Gibbs free energy calculated by applying mol. mechanics interaction energies was compared with the one obtained by using exptl. inhibitory potencies for a series of HIV protease inhibitors, and a fairly good correlation was found between the two. Based on this favorable relationship between the computational and the exptl. results, the computational expts. were pursued for the compds. drawn by Sybyl taking into consideration the fact that unexploited carbon affinity regions (or hydrophobic regions) with sizable volume were detected on the docking study of inh1 and inh8 against HIV protease. Those were compds. with a t-Bu substituted by various hydrophobic side chains. Among those a compound with a benzyl group exhibited the lowest docking energy. Since one of the goals of this paper was to perform the computational drug-design experiment to investigate potential HIV protease inhibitors, the authors would like to leave the clin. investigational work for the expertise of those areas.

SUPPL. TERM: HIV protease inhibitor drug design structure activity Gibbs

energy
INDEX TERM: Drug design
Entropy
Free energy
Structure-activity relationship
(docking mode of HIV protease and their inhibitors)
INDEX TERM: 144114-21-6, HIV protease
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(docking mode of HIV protease and their inhibitors)
INDEX TERM: 191849-89-5 **191850-28-9** 191850-29-0
191851-38-4 191851-39-5 191873-63-9 **433709-59-2**
433709-60-5 433709-61-6 433709-62-7
433709-63-8 433709-64-9 433709-65-0
ROLE: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(docking mode of HIV protease and their inhibitors)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD.
REFERENCE(S): (1) Beck, A; Virology 2000, V274, P391
(2) Bini, E; Dig Dis Sci 2000, V45, P1301 HCAPLUS
(3) Bohm, H; J Comput-Aided Mol Design 1992, V6, P593
MEDLINE
(4) Chaom, C; Adv Exp Med Biol 1998, V437, P83
(5) Friedman, S; J Med Chem 1998, V41, P2424 HCAPLUS
(6) Goodsell, D; Proteins Struc Funct 1993, V17, P1 HCAPLUS
(7) Krzysztof, A; Perspectives in Drug Discovery and Design 1993, V1, P23
(8) Kuntz, I; J Mol Biol 1982, V161, P269 HCAPLUS
(9) Lee, T; J Am Chem Soc 1999, V121, P1145 HCAPLUS
(10) Li, M; Proteins 2000, V38, P29 HCAPLUS
(11) Lunney, E; J Med Chem 1994, V37, P2664 HCAPLUS
(12) Morris, G; J Computational Chemistry 1998, V19, P1639 HCAPLUS
(13) Perez, C; J Med Chem 1998, V41, P836 HCAPLUS
(14) Rosin, C; UCSD CSE Technical Report 1997, CS97-522, P1
(15) Stoddard, B; Nature 1992, V358, P774 HCAPLUS
(16) Turner, S; J Med Chem 1998, V42, P3467
(17) Ueda, H; J Clin Invest 1998, V102, P804 HCAPLUS
(18) Wang, J; J Immunol 1998, V161, P4309 HCAPLUS
IT **191850-28-9 433709-59-2 433709-60-5**
433709-61-6
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(docking mode of HIV protease and their inhibitors)
RN 191850-28-9 HCAPLUS
CN Carbamic acid, [3-[(2S,4R)-2-[[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

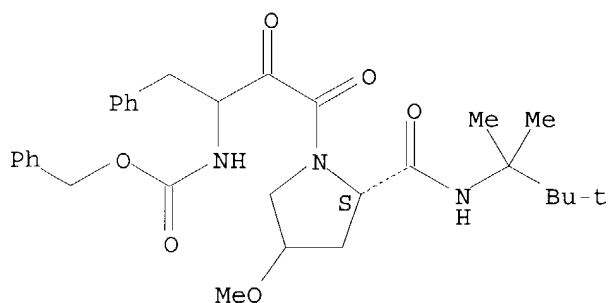
Absolute stereochemistry.



RN 433709-59-2 HCAPLUS

CN Carbamic acid, [3-[(2S)-4-methoxy-2-[[[(1,1,2,2-tetramethylpropyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

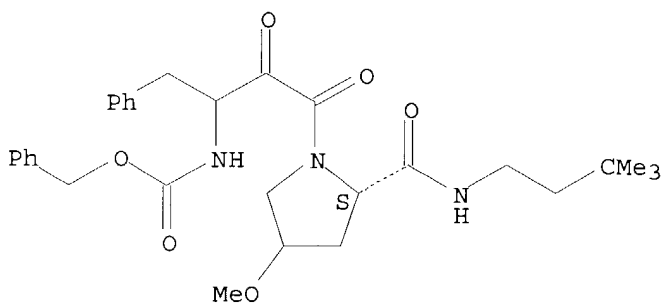
Absolute stereochemistry.



RN 433709-60-5 HCAPLUS

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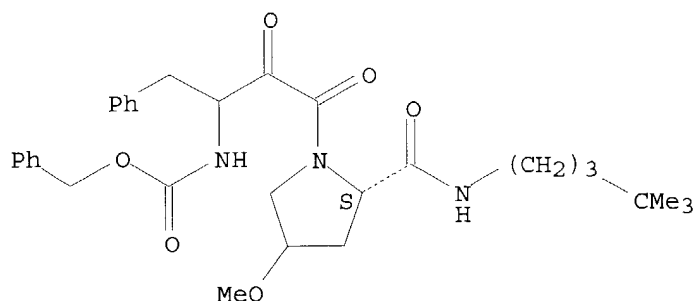
Absolute stereochemistry.



RN 433709-61-6 HCAPLUS

CN Carbamic acid, [3-[(2S)-2-[[[(4,4-dimethylpentyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> diall hitstr l47 2-

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 2 ANSWERS - CONTINUE? Y/(N):y

L47 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1997:473732 HCAPLUS
 DOCUMENT NUMBER: 127:81793
 ENTRY DATE: Entered STN: 30 Jul 1997
 TITLE: Preparation of hydroxyethylamine core structures as
 HIV and FIV protease inhibitors
 INVENTOR(S): Wong, Chi-Huey; Snee, Deborah H.; Laslo, Karen
 PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Snee,
 Deborah H.; Laslo, Karen
 SOURCE: PCT Int. Appl., 202 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 INT. PATENT CLASSIF.:
 MAIN: G01N033-53
 CLASSIFICATION: 34-3 (Amino Acids) d Proteins)
 Section 63
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

Applicants
PCT

PATENT NO.	KIND	NO.	DATE
WO 9721100	A1	71	19961209
W: AL, AM, AT, AU, AZ,		CH, CN, CU, CZ, DE,	
DK, EE, ES, FI, GB,		KG, KP, KR, KZ, LC,	
LK, LR, LS, LT, LU,		RU, MA, MN, MW, MX, NO, NZ, PL, PT,	
RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN,			
AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,			
IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML,			
MR, NE, SN, TD, TG			
CA 2238337	AA	19970612	CA 1996-2238337 19961209
AU 9712844	A1	19970627	AU 1997-12844 19961209
AU 728373	B2	20010111	
EP 873519	A1	19981028	EP 1996-943657 19961209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,			
IE, SI, LT, LV, FI, RO			
JP 2000502332	T2	20000229	JP 1997-521485 19961209

PRIORITY APPLN. INFO.:

US 1995-568532

A2 19951207

WO 1996-US19571

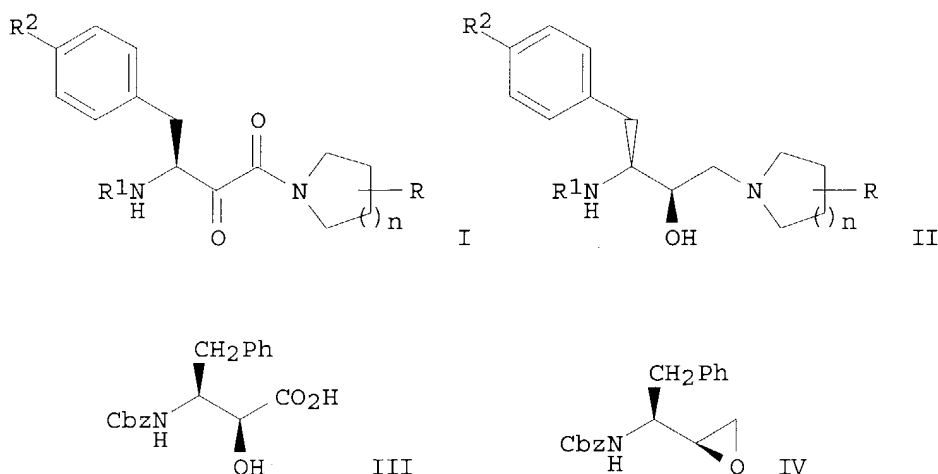
W 19961209

PATENT CLASSIFICATION CODES:

PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES

WO 9721100 ICM G01N033-53
 OTHER SOURCE(S): MARPAT 127:81793

GRAPHIC IMAGE:



ABSTRACT:

Combinatorial libraries of HIV and FIV protease inhibitors are characterized by α -keto amide or hydroxyethylamine core structures I and II [$n = 1, 2$; $R =$ one or more groups CONHMe_3 , CH_2OH , CH_2OMe , $\text{CH}_2\text{OCH}_2\text{Ph}$, OH , OCH_2Ph , C1-4 alkoxy , optionally nitro-substituted 2-, 3-, or 4- $\text{MeOC}_6\text{H}_4\text{CH}_2\text{O}$, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; $R_1 = \text{PhCH}_2\text{O}_2\text{C}$ (Cbz), $\text{Me}_3\text{CO}_2\text{C}$ (Boc), acyl; $R_2 = \text{H}$, HO , PhCH_2O , C1-4 alkoxy , optionally nitro-substituted 2-, 3-, or 4- $\text{MeOC}_6\text{H}_4\text{CH}_2\text{O}$, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidation to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for binding and inhibitory activity against both HIV and FIV protease. Drug candidates displaying clin. useful activity against both HIV and FIV protease are identified as being potentially resistive against a loss of inhibitory activity due to development of resistant strains of HIV.

SUPPL. TERM:

hydroxyethylamine peptidomimetic prepn HIV protease inhibitor; FIV protease inhibitor ketoamide peptidomimetic prepn; combinatorial peptidomimetic library prepn protease inhibitor

INDEX TERM:

Carbohydrates, preparation

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(amino sugars; preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

INDEX TERM:

Peptidomimetics

ROLE: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (mixts.; preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

INDEX TERM: Combinatorial library
 Feline immunodeficiency virus
 Human immunodeficiency virus 1
 (preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

INDEX TERM: 37205-61-1, Protease inhibitor
 ROLE: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (HIV and FIV; preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

INDEX TERM: 78169-47-8, Aspartyl protease
 ROLE: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
 (HIV and FIV; preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

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 172696-16-1P 172696-17-2P 172696-18-3P 172823-16-4P
 172823-17-5P 191849-88-4P 191849-89-5P 191849-90-8P
 191849-95-3P 191849-97-5P 191849-99-7P 191850-01-8P
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191851-43-1P 191873-61-7P 191873-63-9P
 ROLE: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

INDEX TERM: 191850-98-3P 191851-04-4P 191851-45-3P
 ROLE: BPN (Biosynthetic preparation); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

INDEX TERM: 51-35-4, trans-4-Hydroxy-L-proline 63-91-2,
 L-Phenylalanine, reactions 75-64-9, tert-Butylamine,

reactions 147-85-3, L-Proline, reactions 618-27-9,
 cis-4-Hydroxy-L-proline 623-05-2, p-Hydroxybenzyl alcohol
 2133-40-6, L-Proline methyl ester hydrochloride 2577-48-2
 3958-60-9, o-Nitrobenzyl bromide 4298-08-2 13504-86-4
 15761-39-4 19130-96-2 100937-52-8 102508-03-2
 121253-57-4 128019-01-2 132295-44-4 136465-98-0
 161723-80-4 172823-19-7 191849-93-1 191850-53-0
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ROLE: RCT (Reactant); RACT (Reactant or reagent)

(preparation of hydroxyethylamine core structures as HIV and
 FIV protease inhibitors)

INDEX TERM:

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191850-44-9P	191850-45-0P	191850-46-1P	191850-47-2P
191850-48-3P	191850-49-4P	191850-50-7P	191850-97-2P
191850-99-4P	191851-00-0P	191851-01-1P	191851-02-2P
191851-05-5P	191851-06-6P	191851-07-7P	191851-08-8P
191851-09-9P	191851-10-2P	191851-11-3P	191851-12-4P
191851-13-5P	191851-14-6P	191851-15-7P	191851-16-8P
191851-17-9P	191851-18-0P	191851-19-1P	191851-20-4P
191851-21-5P	191851-22-6P	191851-23-7P	191851-24-8P
191851-25-9P	191851-26-0P	191851-27-1P	191851-28-2P
191851-29-3P	191851-30-6P	191851-31-7P	191851-32-8P
191851-33-9P	191851-34-0P	191851-35-1P	191851-36-2P
191851-44-2P	191851-46-4P	191851-47-5P	191851-48-6P
191851-49-7P	191851-50-0P	191851-51-1P	
191851-52-2P	191851-55-5P	191851-56-6P	191851-57-7P
191851-58-8P	191851-59-9P	191851-60-2P	191851-61-3P
191851-62-4P	191851-64-6P	191851-66-8P	191851-67-9P
191851-73-7P	191851-74-8P	191851-75-9P	191851-76-0P
191851-77-1P	191851-78-2P	191851-79-3P	191851-80-6P
191851-82-8P	191851-83-9P	191851-84-0P	191851-85-1P
191851-86-2P	191851-89-5P	191851-91-9P	191851-93-1P
191852-04-7P	191852-06-9P	191852-19-4P	191852-23-0P

ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
 (Preparation); RACT (Reactant or reagent)

(preparation of hydroxyethylamine core structures as HIV and
 FIV protease inhibitors)

IT 191850-27-8P 191850-28-9P 191850-30-3P
 191850-32-5P 191850-33-6P 191850-34-7P
 191850-35-8P 191850-36-9P 191850-37-0P
 191850-38-1P 191850-59-6P 191850-61-0P
 191850-91-6P 191850-92-7P 191850-93-8P
 191850-94-9P 191850-95-0P 191850-96-1P
 191851-37-3P 191851-42-0P 191851-43-1P

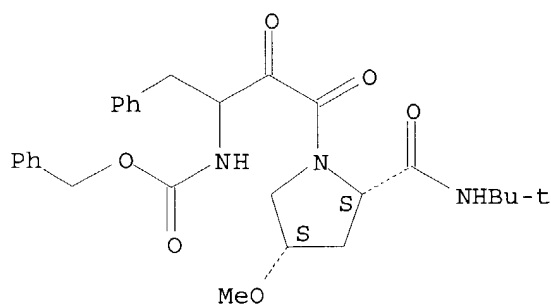
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

RN 191850-27-8 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,4 α)]-[partial]- (9CI) (CA INDEX NAME)

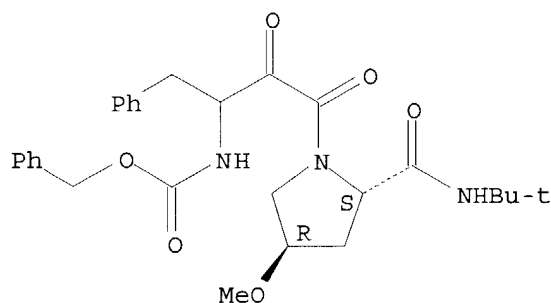
Absolute stereochemistry.



RN 191850-28-9 HCAPLUS

CN Carbamic acid, [3-[(2S,4R)-2-[[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

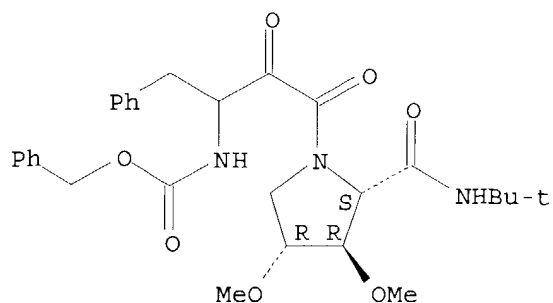
Absolute stereochemistry.



RN 191850-30-3 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dimethoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,3 β ,4 α)]-[partial]- (9CI) (CA INDEX NAME)

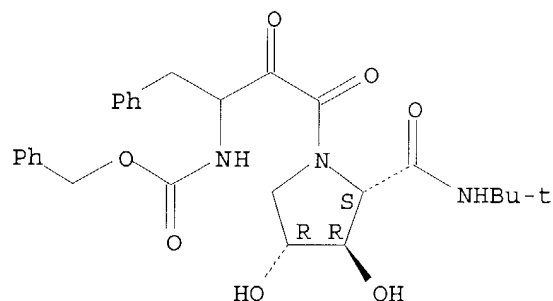
Absolute stereochemistry.



RN 191850-32-5 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dihydroxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,3 β ,4 α)]-[partial]- (9CI) (CA INDEX NAME)

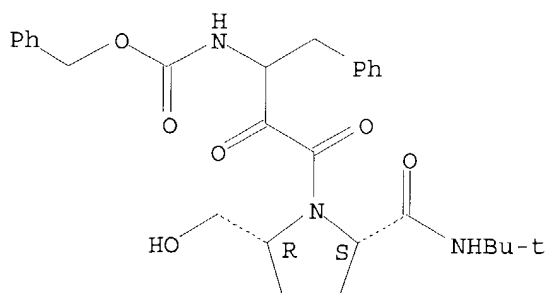
Absolute stereochemistry.



RN 191850-33-6 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-5-(hydroxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,5 α)]-[partial]- (9CI) (CA INDEX NAME)

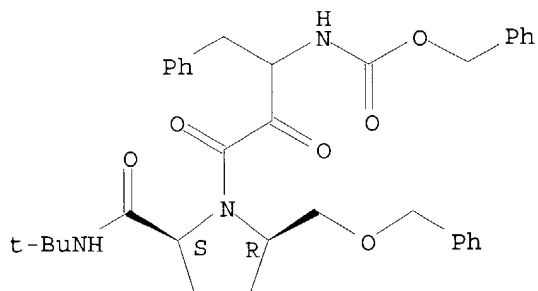
Absolute stereochemistry.



RN 191850-34-7 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-5-[(phenylmethoxy)methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,5 α)]-[partial]- (9CI) (CA INDEX NAME)

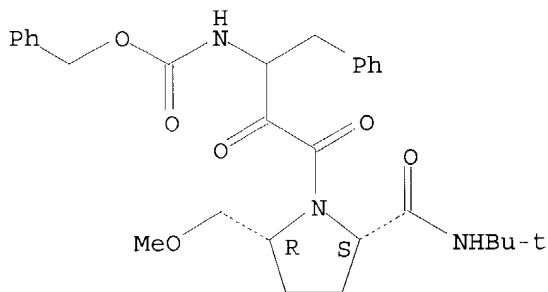
Absolute stereochemistry.



RN 191850-35-8 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2α,5α)]-[partial]- (9CI) (CA INDEX NAME)

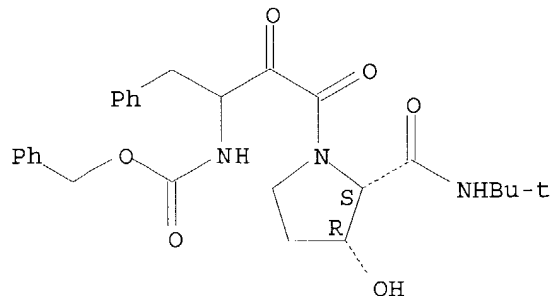
Absolute stereochemistry.



RN 191850-36-9 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3-hydroxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2α,3α)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

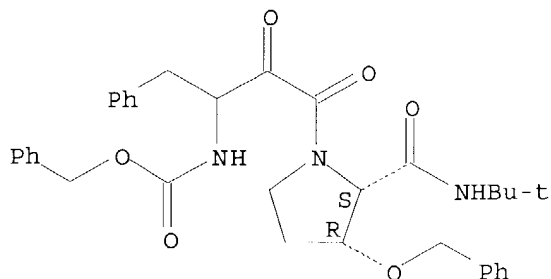


RN 191850-37-0 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2α,3α)]-[partial]- (9CI) (CA INDEX NAME)

phenylmethyl ester, [2S-(2 α ,3 α)]-[partial]- (9CI) (CA INDEX NAME)

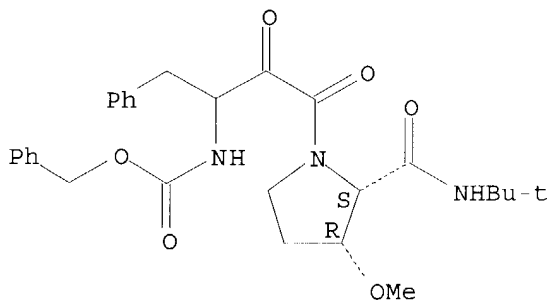
Absolute stereochemistry.



RN 191850-38-1 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,3 α)]-[partial]- (9CI) (CA INDEX NAME)

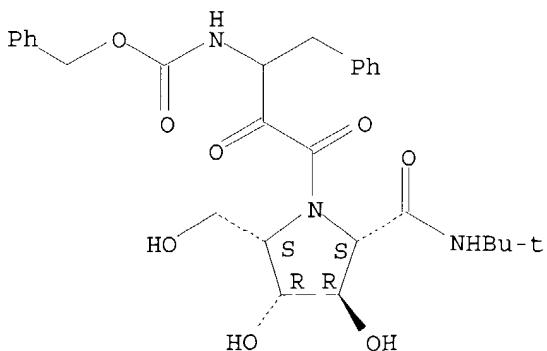
Absolute stereochemistry.



RN 191850-59-6 HCAPLUS

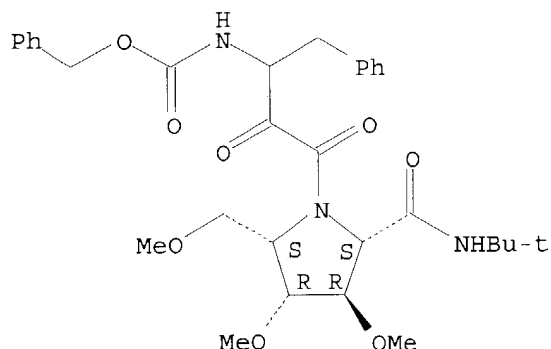
CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dihydroxy-5-(hydroxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,3 β ,4 α ,5 α)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



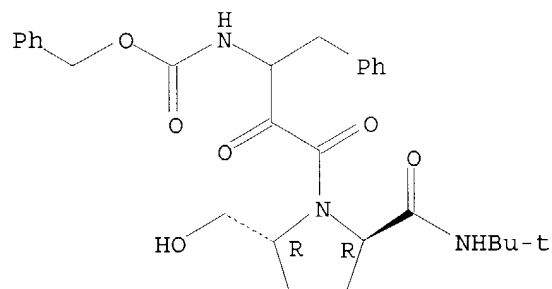
RN 191850-61-0 HCAPLUS
 CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dimethoxy-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,3 β ,4 α ,5 α)]-[partial]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



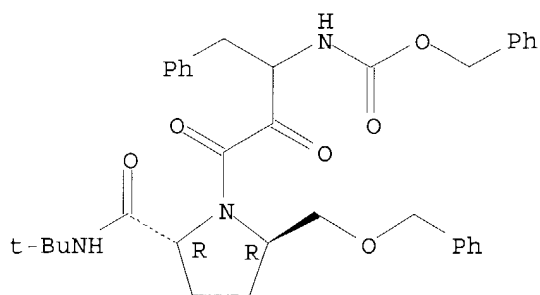
RN 191850-91-6 HCAPLUS
 CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-5-(hydroxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2 α ,5 β)]-[partial]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-92-7 HCAPLUS
 CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-5-[(phenylmethoxy)methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2 α ,5 β)]-[partial]-(9CI) (CA INDEX NAME)

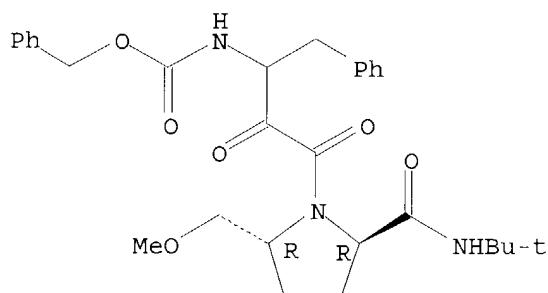
Absolute stereochemistry.



RN 191850-93-8 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2 α ,5 β)]-[partial]- (9CI) (CA INDEX NAME)

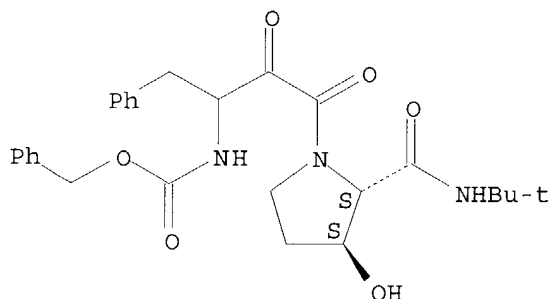
Absolute stereochemistry.



RN 191850-94-9 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3-hydroxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,3 β)]-[partial]- (9CI) (CA INDEX NAME)

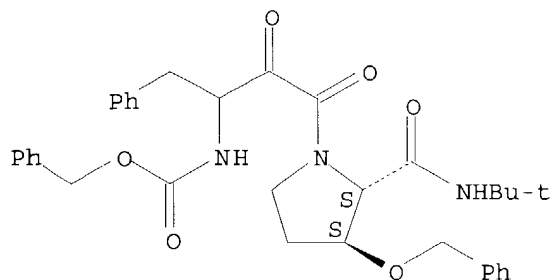
Absolute stereochemistry.



RN 191850-95-0 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,3 β)]-[partial]- (9CI) (CA INDEX NAME)

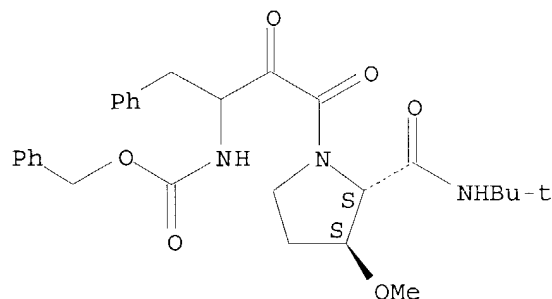
Absolute stereochemistry.



RN 191850-96-1 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2α,3β)]-[partial]-(9CI) (CA INDEX NAME)

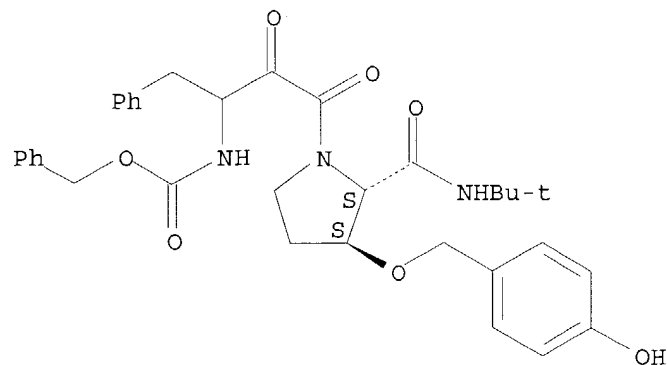
Absolute stereochemistry.



RN 191851-37-3 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3-[(4-hydroxyphenyl)methoxy]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2α,3β)]-[partial]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

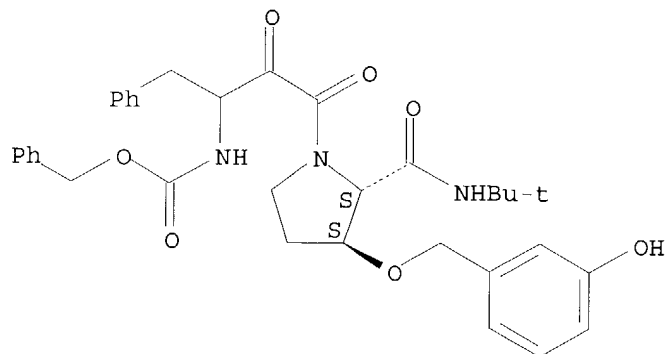


RN 191851-42-0 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-3-[(3-

hydroxyphenyl)methoxy]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,3 β)]-[partial]- (9CI) (CA INDEX NAME)

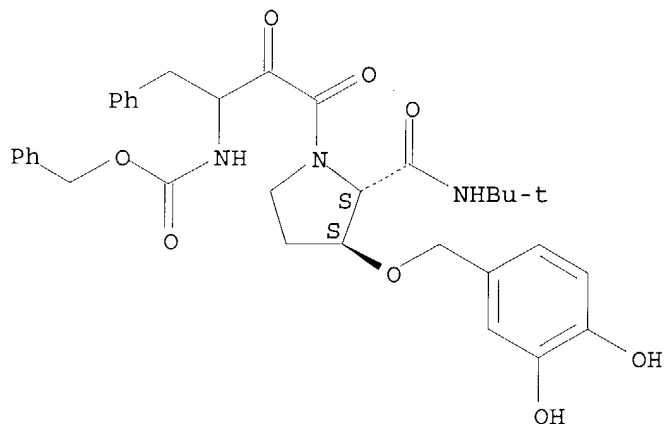
Absolute stereochemistry.



RN 191851-43-1 HCAPLUS

CN Carbamic acid, [3-[3-[(3,4-dihydroxyphenyl)methoxy]-2-[[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,3 β)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **191851-51-1P**

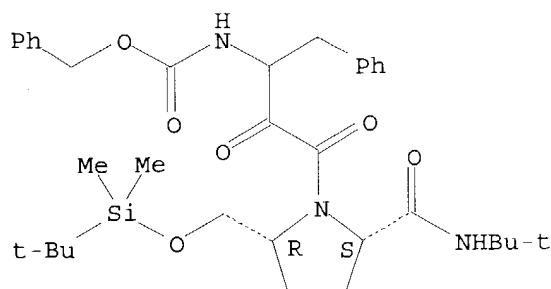
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

RN 191851-51-1 HCAPLUS

CN Carbamic acid, [3-[2-[[[(1,1-dimethylethyl)amino]carbonyl]-5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2 α ,5 α)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L47 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:938815 HCAPLUS

DOCUMENT NUMBER: 124:105570

ENTRY DATE: Entered STN: 23 Nov 1995

TITLE: Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing α -Keto Amide and Hydroxyethylamine Core StructuresAUTHOR(S): Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey
CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1995), 117(48), 11867-78

CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

CLASSIFICATION: 1-3 (Pharmacology)

Section cross-reference(s): 28, 34

ABSTRACT:

This study describes the development of new pyrrolidine-containing α -keto amide and hydroxyethylamine core structures. The study shows that the HIV and FIV protease inhibition is 300-fold better than the hydroxyethylamine isosteric structure and 1300-fold better than the phosphinic acid derivative as an inhibitor of the HIV protease. The study is however not hydrated. The study is indicated by the NMR study and the inhibition activities of the prepared pyrrolidine derivatives. The study revealed that the prepared pyrrolidine derivatives could improve the binding 5- and 10-fold. The study revealed that the prepared pyrrolidine derivatives could improve the binding 5- and 10-fold. The study revealed that the prepared pyrrolidine derivatives could improve the binding 5- and 10-fold.

Applicants

* note

entry
date

in STN

SUPPL. TERM:

pr
st
pr
MO
RO
unamide hydroxyethylamine prepn
inhibitor pyrrolidine ketoamide

INDEX TERM:

local activity relationship
study; BSU (Biological study,
chemical study); PROC (Process)(protease-inhibiting, of pyrrolidine-containing
 α -keto amide and hydroxyethylamines)

INDEX TERM:

141197-75-3P

ROLE: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); PRP (Properties); SPN
 (Synthetic preparation); THU (Therapeutic use); BIOL
 (Biological study); PREP (Preparation); USES (Uses)
 (HIV and FIV proteases inhibition by pyrrolidine-containing
 α -keto amide and hydroxyethylamines)
 INDEX TERM: 128018-20-2P 172696-13-8P 172696-14-9P 172696-15-0P
 172696-16-1P 172696-17-2P 172696-18-3P 172696-19-4P
 172696-30-9P 172823-16-4P 172823-17-5P 172883-15-7P
 172953-21-8P
 ROLE: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); SPN (Synthetic
 preparation); THU (Therapeutic use); BIOL (Biological
 study); PREP (Preparation); USES (Uses)
 (HIV and FIV proteases inhibition by pyrrolidine-containing
 α -keto amide and hydroxyethylamines)
 INDEX TERM: 161723-79-1
 ROLE: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); THU (Therapeutic use);
 BIOL (Biological study); USES (Uses)
 (HIV and FIV proteases inhibition by pyrrolidine-containing
 α -keto amide and hydroxyethylamines)
 INDEX TERM: 15761-39-4
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (amidation of)
 INDEX TERM: 114744-85-3 128018-44-0 172696-27-4 172696-28-5
 172823-19-7 173009-88-6
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (in preparation of pyrrolidine-containing α -keto amide and
 hydroxyethylamines as protease inhibitors)
 INDEX TERM: 62023-59-0P 62023-60-3P 63126-47-6P 121253-53-0P
 121253-57-4P 128018-18-8P 172696-20-7P 172696-21-8P
 172696-22-9P 172696-23-0P 172696-24-1P 172696-25-2P
 172696-26-3P 172696-29-6P 172823-18-6P 172823-20-0P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
 (Preparation); RACT (Reactant or reagent)
 (in preparation of pyrrolidine-containing α -keto amide and
 hydroxyethylamines as protease inhibitors)
 INDEX TERM: 9001-92-7, Protease
 ROLE: BPR (Biological process); BSU (Biological study,
 unclassified); BIOL (Biological study); PROC (Process)
 (inhibitors; HIV and FIV proteases inhibition by
 pyrrolidine-containing α -keto amide and
 hydroxyethylamines)
 INDEX TERM: 68030-64-8P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
 (Preparation); RACT (Reactant or reagent)
 (preparation and deprotection of)
 INDEX TERM: 172696-32-1P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
 (Preparation); RACT (Reactant or reagent)
 (preparation and hydrogenolysis of)
 INDEX TERM: 172696-31-0P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
 (Preparation); RACT (Reactant or reagent)
 (preparation and oxidation of)
 INDEX TERM: 172823-21-1P
 ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP
 (Preparation); RACT (Reactant or reagent)
 (preparation and protection of)

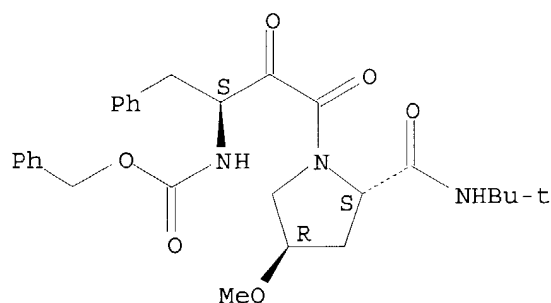
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 172696-34-3P 172823-22-2P **172823-23-3P**
 172823-24-4P 172823-25-5P
 ROLE: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); SPN (Synthetic
 preparation); THU (Therapeutic use); BIOL (Biological
 study); PREP (Preparation); USES (Uses)
 (reaction with benzyloxycarbonyl chloride)

INDEX TERM: 172823-15-3
 ROLE: RCT (Reactant); RACT (Reactant or reagent)
 (reaction with benzyloxycarbonyl chloride)

IT **172696-33-2P 172823-23-3P**
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
 BIOL (Biological study); PREP (Preparation); USES (Uses)
 (reaction with benzyloxycarbonyl chloride)

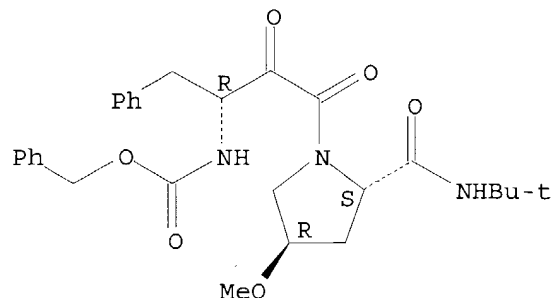
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 [2S-[1(R*),2 α ,4 β]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



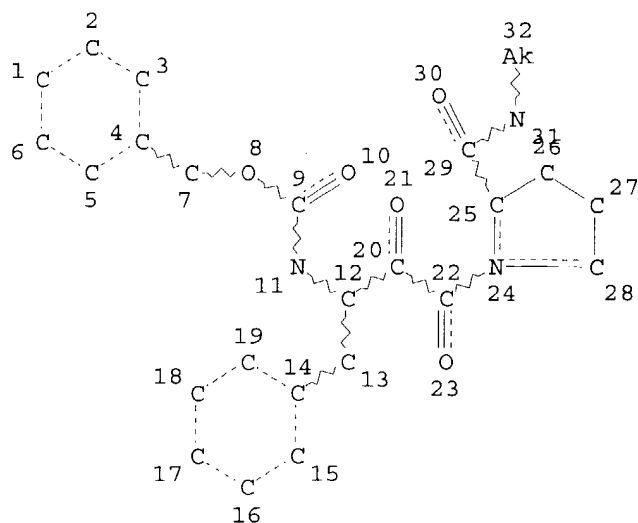
RN 172823-23-3 HCAPLUS
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 pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester,
 [2S-[1(S*),2 α ,4 β]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d que 154
 L31

STR



NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

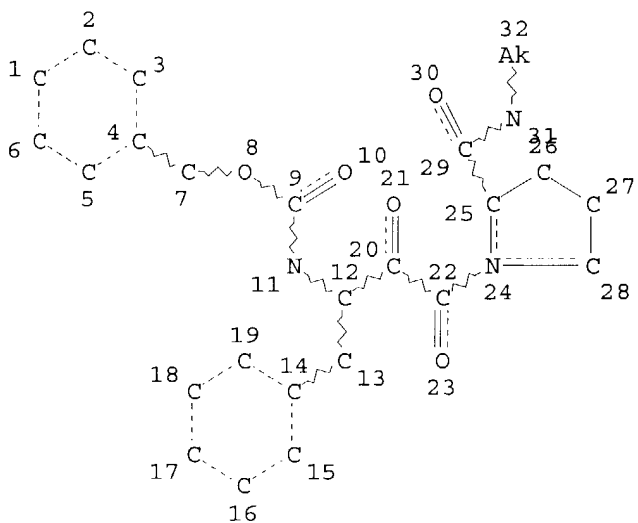
RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE

L37

STR



NODE ATTRIBUTES:

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CONNECT IS E2 RC AT 27

CONNECT IS E2 RC AT 28

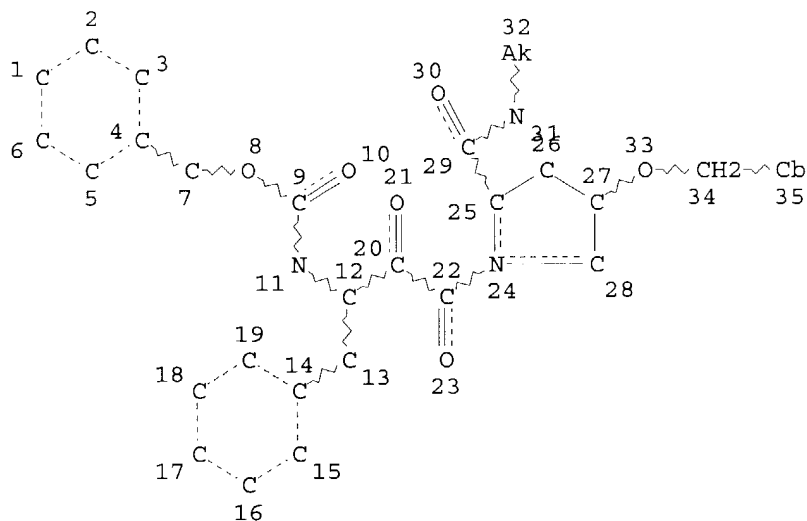
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GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE
L42 STR



NODE ATTRIBUTES:
CONNECT IS E1 RC AT 35
DEFAULT MLEVEL IS ATOM
GGCAT IS MCY UNS AT 35
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E6 C AT 35

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE
L49 10 SEA FILE=BEILSTEIN SSS FUL L31
L51 4 SEA FILE=BEILSTEIN SSS FUL L37
L52 4 SEA FILE=BEILSTEIN SSS FUL L42
L53 2 SEA FILE=BEILSTEIN ABB=ON PLU=ON L49 NOT (L51 OR L52)
L54 2 SEA FILE=BEILSTEIN ABB=ON PLU=ON L53 NOT RN/FA

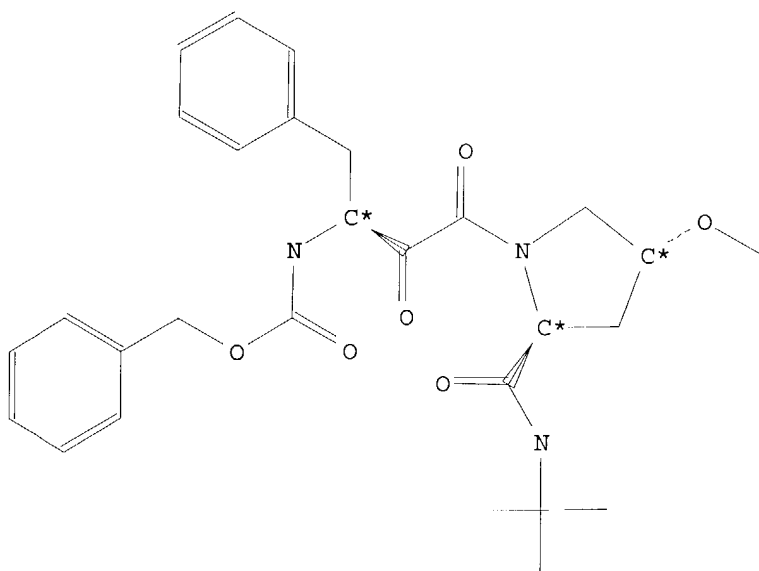
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YOU HAVE REQUESTED DATA FROM FILE 'BEILSTEIN' - CONTINUE? (Y)/N:y

L54 ANSWER 1 OF 2 BEILSTEIN COPYRIGHT 2004 BEILSTEIN MDL on STN

Beilstein Records (BRN):	7470947
Chemical Name (CN):	(3S)-3-(N-benzyloxycarbonyl)amino-2-keto-4-phenylbutyryl-<2'(S)-(tert-butylamido)-4'(R)-methoxy>pyrrolidine
Autonom Name (AUN):	<1-benzyl-3-(2-tert-butylcarbamoyl-4-methoxy-pyrrolidin-1-yl)-2,3-dioxo-propyl>-carbamic acid benzyl ester

Molec. Formula (MF): C28 H35 N3 O6
 Molecular Weight (MW): 509.60
 Lawson Number (LN): 26641, 16298, 5228, 2846, 1762, 289
 File Segment (FS): Stereo compound
 Compound Type (CTYPE): heterocyclic
 Constitution ID (CONSID): 6382977
 Tautomer ID (TAUTID): 7081158
 Beilstein Citation (BSO): 6-22
 Entry Date (DED): 1996/08/09
 Update Date (DUPD): 1997/04/28



Field Availability:

Code	Name	Occurrence
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	6
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
ED	Entry Date	1
UPD	Update Date	1
NMR	Nuclear Magnetic Resonance	3

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
------	------	------------

```
=====
RX          Reaction Documents                      1
RXPRO       Substance is Reaction Product          1
```

=> d l54 rx 1

YOU HAVE REQUESTED DATA FROM FILE 'BEILSTEIN' - CONTINUE? (Y)/N:y

L54 ANSWER 1 OF 2 BEILSTEIN COPYRIGHT 2004 BEILSTEIN MDL on STN

Reaction:

RX

```
Reaction ID (.ID):          4451693
Reactant BRN (.RBRN):      7451583
Reactant (.RCT):           <1-benzyl-3-(2-tert-butylcarbamoyl-4-
                           methoxy-pyrrolidin-1-yl)-2-hydroxy-3-oxo-
                           propyl>-carbamic acid benzyl ester
Product BRN (.PBRN):       7470947, 7470946
Product (.PRO):            (3S)-3-(N-benzyloxycarbonyl)amino-2-keto-4-
                           phenylbutyryl-<2'(S)-(tert-butylamido)-
                           4'(R)-methoxy>pyrrolidine,
                           (3R)-3-(N-benzyloxycarbonyl)amino-2-keto-4-
                           phenylbutyryl-<2'(S)-(tert-butylamido)-
                           4'(R)-methoxy>pyrrolidine
No. of React. Details (.NVAR): 1
```

Reaction Details:

RX

```
Reaction RID (.RID):        4451693.1
Reaction Classification (.CL): Preparation
Reagent (.RGT):            Dess-Martin periodinane
Solvent (.SOL):            CH2Cl2
Time (.TIM):               24 hour(s)
Other Conditions (.COND):   Ambient temperature
Note(s) (.COM):            Yield given. Yields of byproduct given.
                           Title compound not separated from
                           byproducts
Reference(s):
1. Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.;
   Gustchina, Alla; et al., J.Amer.Chem.Soc., CODEN: JACSAT, 117(48),
   <1995>, 11867-11878; BABS-6008352
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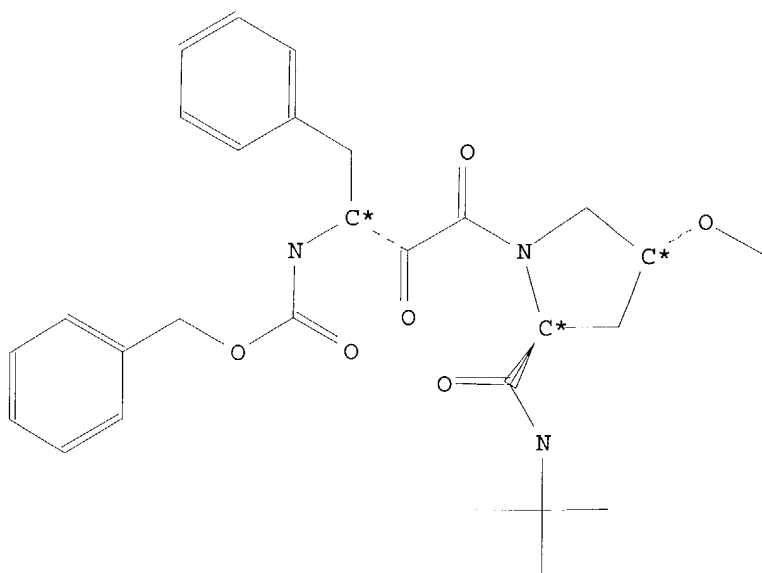
=> d l54 ide 2

YOU HAVE REQUESTED DATA FROM FILE 'BEILSTEIN' - CONTINUE? (Y)/N:y

L54 ANSWER 2 OF 2 BEILSTEIN COPYRIGHT 2004 BEILSTEIN MDL on STN

```
Beilstein Records (BRN):    7470946
Chemical Name (CN):         (3R)-3-(N-benzyloxycarbonyl)amino-2-keto-4-
                           phenylbutyryl-<2'(S)-(tert-butylamido)-
                           4'(R)-methoxy>pyrrolidine
Autonom Name (AUN):        <1-benzyl-3-(2-tert-butylcarbamoyl-4-
                           methoxy-pyrrolidin-1-yl)-2,3-dioxo-propyl>-
```

Molec. Formula (MF): carbamic acid benzyl ester
 C28 H35 N3 O6
 Molecular Weight (MW): 509.60
 Lawson Number (LN): 26641, 16298, 5228, 2846, 1762, 289
 File Segment (FS): Stereo compound
 Compound Type (CTYPE): heterocyclic
 Constitution ID (CONSID): 6382977
 Tautomer ID (TAUTID): 7081158
 Beilstein Citation (BSO): 6-22
 Entry Date (DED): 1996/08/09
 Update Date (DUPD): 1997/04/28



Field Availability:

Code	Name	Occurrence
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	6
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
ED	Entry Date	1
UPD	Update Date	1
NMR	Nuclear Magnetic Resonance	2

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
=====		

RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

=> d l54 rx 2

YOU HAVE REQUESTED DATA FROM FILE 'BEILSTEIN' - CONTINUE? (Y)/N:y

L54 ANSWER 2 OF 2 BEILSTEIN COPYRIGHT 2004 BEILSTEIN MDL on STN

Reaction:

RX

Reaction ID (.ID):	4451693
Reactant BRN (.RBRN):	7451583
Reactant (.RCT):	<1-benzyl-3-(2-tert-butylcarbamoyl-4-methoxy-pyrrolidin-1-yl)-2-hydroxy-3-oxo-propyl>-carbamic acid benzyl ester
Product BRN (.PBRN):	7470947, 7470946
Product (.PRO):	(3S)-3-(N-benzyloxycarbonyl)amino-2-keto-4-phenylbutyryl-<2'(S)-(tert-butylamido)-4'(R)-methoxy>pyrrolidine, (3R)-3-(N-benzyloxycarbonyl)amino-2-keto-4-phenylbutyryl-<2'(S)-(tert-butylamido)-4'(R)-methoxy>pyrrolidine
No. of React. Details (.NVAR):	1

Reaction Details:

RX

Reaction RID (.RID):	4451693.1
Reaction Classification (.CL):	Preparation
Reagent (.RGT):	Dess-Martin periodinane
Solvent (.SOL):	CH2Cl2
Time (.TIM):	24 hour(s)
Other Conditions (.COND):	Ambient temperature
Note(s) (.COM):	Yield given. Yields of byproduct given. Title compound not separated from byproducts

Reference(s):

1. Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; et al., J.Amer.Chem.Soc., CODEN: JACSAT, 117(48), <1995>, 11867-11878; BABS-6008352

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VOLUME 117, NUMBER 48
DECEMBER 6, 1995

JACS A1 117(48) 11823-12018 (1995)
ISSN 0002-7863

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James A. Ramsden, Atta M. Arif, and J. A. Gladysz*

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MOST RECENT CITATIONS FOR PATENTS FROM FIVE MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US 6759447 06 JUL 2004
DE 10353658 09 JUN 2004
EP 1435545 07 JUL 2004
JP 2004198786 15 JUL 2004
WO 2004058765 15 JUL 2004

Structure search limits have been raised. See HELP SLIMIT for the new,
higher limits.

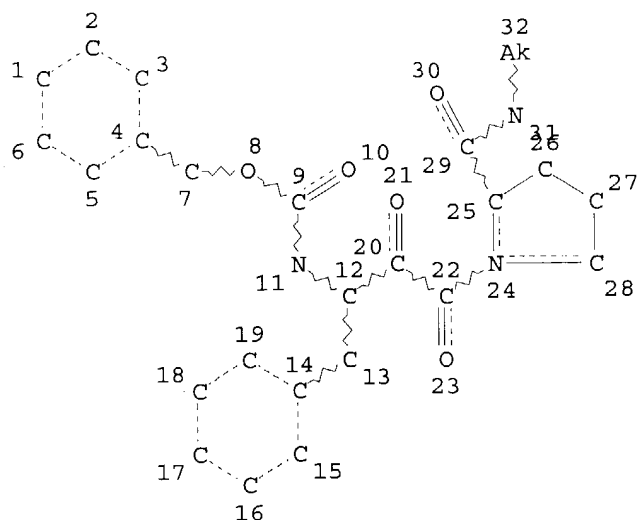
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LAST RELOADED: Aug 20, 2004 (20040820/UP).

=> => d que 157

L31 STR



L31
STR

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 32

STEREO ATTRIBUTES: NONE
L57 2 SEA FILE=MARPAT SSS FUL L31

=> d l57 ibib abs hit
YOU HAVE REQUESTED DATA FROM FILE 'MARPAT' - CONTINUE? (Y)/N:y

L57 ANSWER 1 OF 2 MARPAT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 135:236450 MARPAT
TITLE: Prolyl ester compound inhibitors of rotamase activity,
their preparation, and their use
INVENTOR(S): Hamilton, Gregory S.; Steiner, Joseph P.
PATENT ASSIGNEE(S): GPI NIL Holdings, Inc., USA
SOURCE: U.S., 20 pp., Cont.-in-part of U. S. 693,003.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

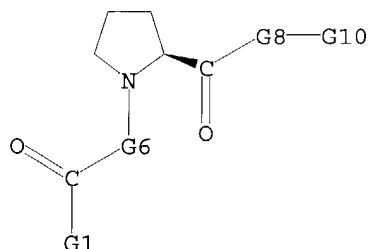
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6291510	B1	20010918	US 1998-73962	19980507
US 5614547	A	19970325	US 1995-479436	19950607
PRIORITY APPLN. INFO.:			US 1995-479436	19950607
			US 1996-693003	19960806

AB The invention provides neurotrophic compds. having an affinity for FKBP-type immunophilins, their preparation, and their use as inhibitors of the

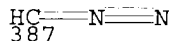
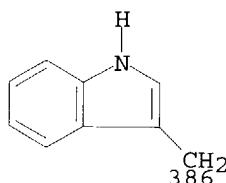
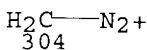
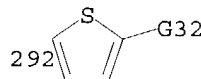
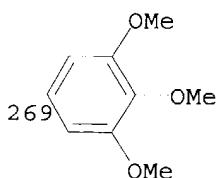
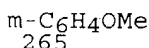
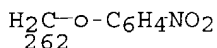
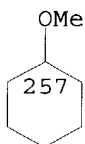
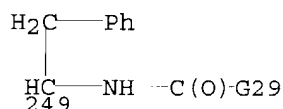
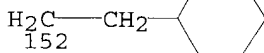
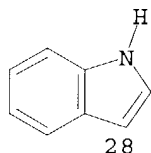
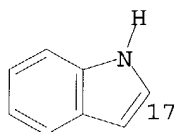
enzyme activity associated with immunophilin proteins, and particularly inhibitors of peptidyl-prolyl isomerase or rotamase enzyme activity. The compds. of the invention may be used in the treatment of neurol. disorders, the prevention of neurodegeneration, and the promotion of neuronal regeneration and growth.

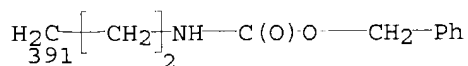
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

MSTR 1



G1 = alkyl<(1-)> (SO G2) / alkenyl<(2-)> (SO G2) / cycloalkyl<(3-5)> (SO G3) / cycloalkenyl<(5-7)> (SO G3) / naphthyl / 17 / 28 / furyl / 2-thiazolyl / thienyl / pyridyl / Ph (SO (1-3) G4) / Cb<EC (10) C, AR (1-), BD (ALL) N, RC (2), RS (2) E6> (SO (1-3) G4) / Hy<EC (0-) N (0-) O (0-) S (0) OTHERQ, AR (1-), RS (0-) E5 (0-) E6 (0) OTHER> (SO (1-3) G4) / (EX C(Me)2CH2Me / Bu-t / 152 / cyclohexyl / 249 / 257 / Et / 262 / 265 / 269 / 292 / 304 / 387 / Pr-n / Me / 386 / Bu-i / 361 / CH2Ph / 391)

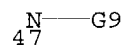




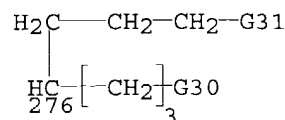
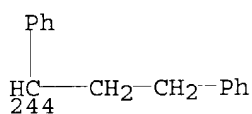
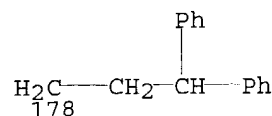
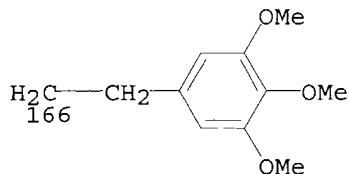
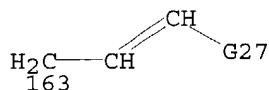
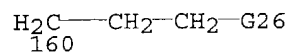
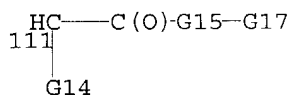
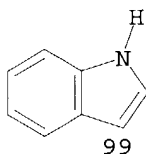
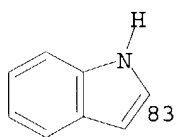
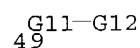
G2 = cycloalkyl<(3-8)> / OH / Ph (SO) /
 Cb<EC (10) C, AR (1-), BD (ALL) N, RC (2), RS (2) E6> (SO) /
 Hy<EC (0-) N (0-) O (0-) S (0) OTHERQ, AR (1-),
 RS (0-) E5 (0-) E6 (0) OTHER> (SO)
 G3 = alkyl<(1-4)> / alkenyl<(2-4)> / OH
 G4 = X / OH / NO2 / CF3 / alkyl<(1-6)> / alkenyl<(2-6)> /
 alkoxy<(1-4)> / alkenyloxy<(2-4)> / OPh / OCH2Ph / NH2
 G6 = **45** / CH2

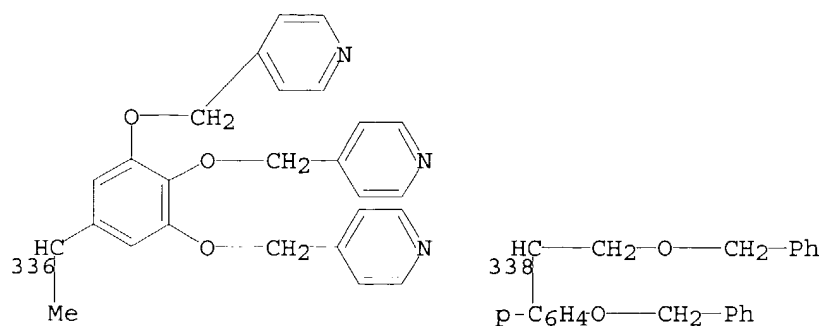


G7 = O / S / CH2
 G8 = O / **NH** / 47

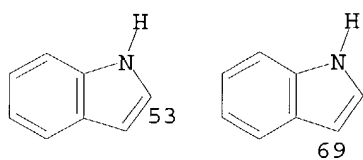


G9 = alkyl<(1-6)>
 G10 = alkyl<(2-6)> (SR (1-) G13) / alkenyl<(2-6)> /
 cycloalkyl<(3-8)> / 49 / 83 / 99 / furyl / 2-thiazolyl /
 thienyl / pyridyl / Ph (SO (1-3) G4) / **111** / (EX 160 / 163 /
 166 / 178 / 244 / Me / Et / CH2Ph / Bu-t / 276 / 336 / 338 /
 Pr-i)

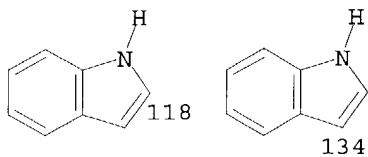




G11 = alkylene<(1-6)> / alkenylene<(2-6)>
 G12 = cycloalkyl
 G13 = naphthyl / 53 / 69 / furyl / 2-thiazolyl / thienyl /
 pyridyl / Ph (SO (1-3) G4) / R



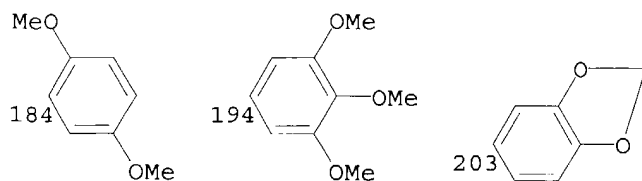
G14 = **alkyl**<(1-8)> (SO G33) / naphthyl / 118 / 134 /
 furyl / 2-thiazolyl / thienyl / pyridyl / Ph (SO (1-3) G4) /
 (EX CH₂Ph)

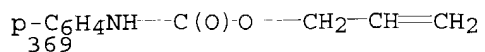


G15 = O / NH / 146

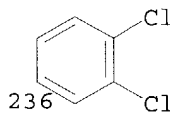
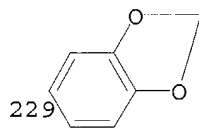
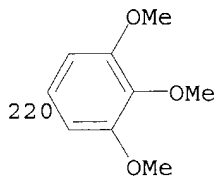
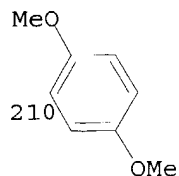
N—G16
 146

G16 = alkyl<(1-6)> / alkenyl<(2-6)>
 G17 = Ph / CH₂Ph / alkyl<(1-5)> (SO Ph) /
 alkenyl<(2-5)> (SO Ph) / (EX Et)
 G26 = 184 / pyridyl / Ph / 194 / 203 / cyclohexyl / 369

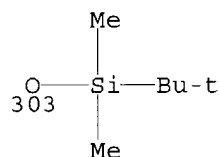




G27 = 210 / Ph / 220 / 229 / cyclohexyl / 236



G28 = OH / 303

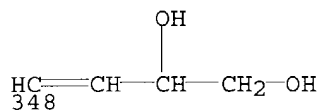
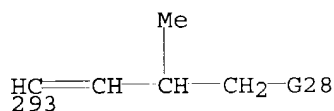


G29 = OBU-t / OCH₂Ph

G30 = 3-pyridyl / 2-pyridyl

G31 = Ph / 3-pyridyl

G32 = 293 / 348



G33 = cycloalkyl<(3-8)> / Cb<EC (10) C, AR (1-),
BD (ALL) N, RC (2), RS (2) E6> (SO) /
Hy<EC (0-) N (0-) O (0-) S (0) OTHERQ, AR (1-),
RS (0-) E5 (0-) E6 (0) OTHER> (SO)
MPL: disclosure
NTE: or pharmaceutically acceptable salts or hydrates
NTE: additional substitution also disclosed

=> d 157 ibib abs hit 2-

YOU HAVE REQUESTED DATA FROM FILE 'MARPAT' - CONTINUE? (Y

YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):

L57 ANSWER 2 OF 2 MARPAT COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 131:45104 MARPAT

TITLE: HIV/FIV protease inhibitors having a small P3 residue

INVENTOR(S): Lee, Taekyu; Wong, Chi-Huey; Elder, John H.

PATENT ASSIGNEE(S): The Scripps Research Institute, USA

SOURCE: PCT Int. Appl., 93 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

*later
date*

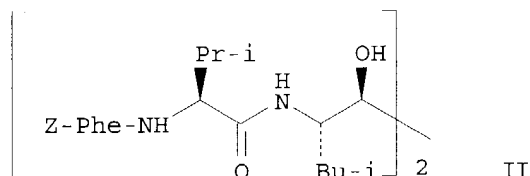
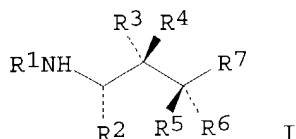
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9929311	A1	19990617	WO 1998-US25964	19981208
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9919045	A1	19990628	AU 1999-19045	19981208
EP 1039886	A1	20001004	EP 1998-963800	19981208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPLN. INFO.:			US 1997-67959P	19971208
			WO 1998-US25964	19981208

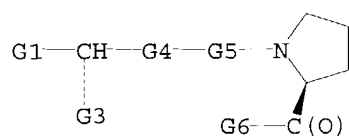
GI



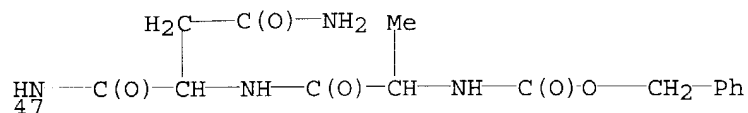
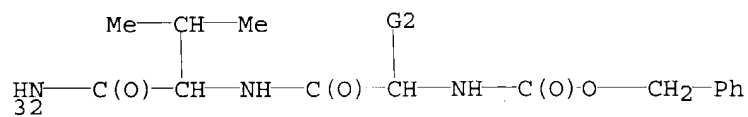
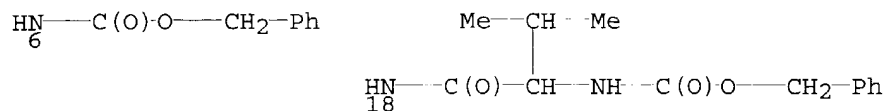
AB Protease inhibitors I [R1 = H, carbobenzyloxy (Z), Z-Val, Z-protected dipeptidyl; R2 = benzyl, isobutyl; R3, R4 H, H; H, OH, O; R5, R6 = H, H; O; R7 = prolinamide or N-tert-butylprolinamide residue] were prepared. Thus, peptidyl diol II was prepared and showed $K_i = 487 \pm 20$ and 5.5 ± 0.8 for inhibition of FIV PR and HIV PR, resp.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

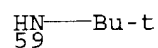
MSTR 1



G1 = NH₂ / 6 / 18 / 32 / 47



G2 = H / Me / Bu-i / CH₂Ph / CH₂OH / CH(OH)Me / Pr-i
 G3 = **CH₂Ph** / Bu-i
 G4 = CH₂ / CHOH / C(O)
 G5 = CH₂ / C(O)
 G6 = NH₂ / 59



MPL: claim 1

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FILE CONTAINS CURRENT INFORMATION.
 LAST RELOADED: Aug 20, 2004 (20040820/UP).

=>

=> fil zcaplus

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FILE COVERS 1907 - 26 Aug 2004 VOL 141 ISS 9
FILE LAST UPDATED: 25 Aug 2004 (20040825/ED)

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=> fil hcaplus

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FILE COVERS 1907 - 26 Aug 2004 VOL 141 ISS 9
FILE LAST UPDATED: 25 Aug 2004 (20040825/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> fil biosis

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CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 18 August 2004 (20040818/ED)

FILE RELOADED: 19 October 2003.

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Aug 20, 2004 (20040820/UP).

=> d que 18

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L5 55 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND ?PROTEAS?
L6 22 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND (AY<1996 OR PY<1996 OR
PRY<1996)
L7 28660 SEA FILE=HCAPLUS ABB=ON PLU=ON (?PROTEAS? (3A) ?INHIBIT?)
L8 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND L7

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L10 9 SEA FILE=BIOSIS ABB=ON PLU=ON ("SLEE D"/AU OR "SLEE D H"/AU)
 OR "SLEE DEBORAH H"/AU

L11 5 SEA FILE=BIOSIS ABB=ON PLU=ON ("LASLO K"/AU OR "LASLO K
 H"/AU OR "LASLO KAREN"/AU OR "LASLO KAREN L"/AU)

L12 1986 SEA FILE=BIOSIS ABB=ON PLU=ON (L9 OR L10 OR L11)

L13 1283 SEA FILE=BIOSIS ABB=ON PLU=ON L12 AND (MY<1996 OR PY<1996)

L14 27485 SEA FILE=BIOSIS ABB=ON PLU=ON (?PROTEAS? (3A) ?INHIBIT?)

L15 1 SEA FILE=BIOSIS ABB=ON PLU=ON L13 AND L14

L16 19 SEA FILE=BIOSIS ABB=ON PLU=ON L13 AND ?PROTEAS?

L19 4 SEA FILE=BIOSIS ABB=ON PLU=ON L16 AND (?PROTEAS? (L)
 ?INHIBIT?)

L22 4 SEA FILE=BIOSIS ABB=ON PLU=ON L15 OR L19

=> dup rem 18 l22

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L55 8 DUP REM L8 L22 (0 DUPLICATES REMOVED)
 ANSWERS '1-4' FROM FILE HCAPLUS
 ANSWERS '5-8' FROM FILE BIOSIS

=> d l55 ibib abs 1-

YOU HAVE REQUESTED DATA FROM 8 ANSWERS - CONTINUE? Y/(N):y

L55 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1997:473732 HCAPLUS
 DOCUMENT NUMBER: 127:81793
 TITLE: Preparation of hydroxyethylamine core structures as
 HIV and FIV **protease inhibitors**
 INVENTOR(S): **Wong, Chi-Huey; Slee, Deborah H.;
 Laslo, Karen**
 PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Slee,
 Deborah H.; Laslo, Karen
 SOURCE: PCT Int. Appl., 202 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 9721100	A1	19970612	WO 1996-US19571	19961209 <--

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

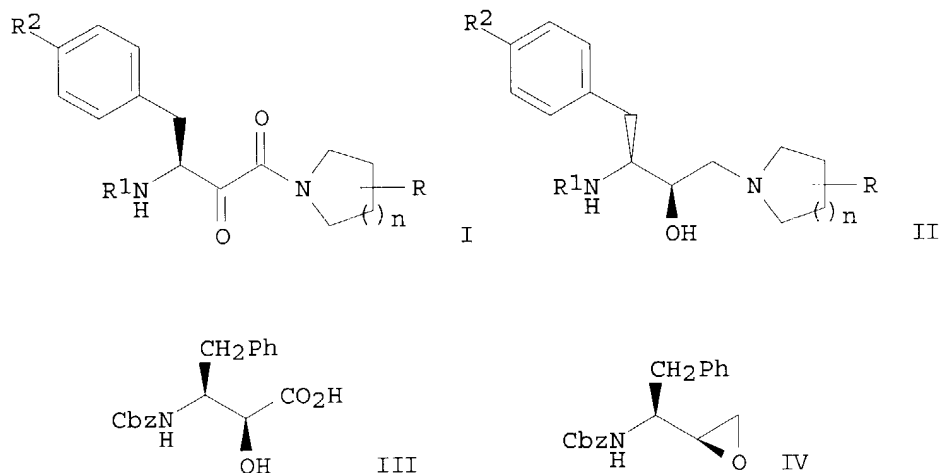
CA 2238337	AA	19970612	CA 1996-2238337	19961209 <--
AU 9712844	A1	19970627	AU 1997-12844	19961209 <--
AU 728373	B2	20010111		
EP 873519	A1	19981028	EP 1996-943657	19961209 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2000502332	T2	20000229	JP 1997-521485	19961209 <--
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PRIORITY APPLN. INFO.:			US 1995-568532	A2 19951207 <--
			WO 1996-US19571	W 19961209

OTHER SOURCE(S): MARPAT 127:81793
GI



AB Combinatorial libraries of HIV and FIV **protease inhibitors** are characterized by α -keto amide or hydroxyethylamine core structures I and II [$n = 1, 2$; $R =$ one or more groups CONHMe_3 , CH_2OH , CH_2OMe , $\text{CH}_2\text{OCH}_2\text{Ph}$, OH , OCH_2Ph , C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4- $\text{MeOC}_6\text{H}_4\text{CH}_2\text{O}$, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; $R_1 = \text{PhCH}_2\text{O}_2\text{C}$ (Cbz), $\text{Me}_3\text{CO}_2\text{C}$ (Boc), acyl; $R_2 = \text{H}$, HO , PhCH_2O , C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4- $\text{MeOC}_6\text{H}_4\text{CH}_2\text{O}$, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidation to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for binding and inhibitory activity against both HIV and FIV **protease**. Drug candidates displaying clinically useful activity against both HIV and FIV **protease** are identified as being potentially resistant against a loss of inhibitory activity due to development of resistant strains of HIV.

L55 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:938815 HCAPLUS

DOCUMENT NUMBER: 124:105570

TITLE: Selectivity in the Inhibition of HIV and FIV
Protease: Inhibitory and Mechanistic
Studies of Pyrrolidine-Containing α -Keto Amide
and Hydroxyethylamine Core Structures

AUTHOR(S): **Slee, Deborah H.; Laslo, Karen L.;**
Elder, John H.; Ollmann, Ian R.; Gustchina, Alla;
Kervinen, Jukka; Zdanov, Alexander; Wlodawer,
Alexander; **Wong, Chi-Huey**

CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1995
, 117(48), 11867-78

CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study describes the development of new pyrrolidine-containing α -keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the HIV and FIV **proteases**. The α -keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the corresponding phosphinic acid derivative as an **inhibitor** of the HIV **protease**. The α -keto amide is however not hydrated until it is bound to the HIV **protease** as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres containing modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepared as **inhibitors** of the HIV **protease**, none show significant **inhibitory** activity against the mechanistically identical FIV **protease**, and addnl. complementary groups are needed to improve inhibition.

L55 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:338480 HCAPLUS

DOCUMENT NUMBER: 122:188156

TITLE: α -Ketoamide Phe-Pro isostere as a new core
structure for the **inhibition** of HIV
protease

AUTHOR(S): Munoz, Benito; Giam, Chou-Zen; **Wong, Chi-Huey**

CORPORATE SOURCE: Dep. Chem., Scripps Res. Inst., La Jolla, CA, 92037,
USA

SOURCE: Bioorganic & Medicinal Chemistry (1994),
2(10), 1085-90

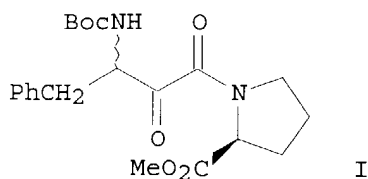
CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB Studies on the **inhibition** of HIV-1 **protease** utilizing a core isostere with replacement of the scissile bond for an α -amino-ketone have resulted in the development of an α -keto-amide isosteric replacement of the Phe-Pro scissile amide bond. The simple dipeptide isostere I was a promising new core structure for the development of the enzyme inhibitors. I exhibited $K_i = 6 \mu\text{M}$ against HIV-1 **protease**, compared to $230 \mu\text{M}$ and $>50 \mu\text{M}$ for the corresponding phosphinic acid and hydroxyethylamine isosteres.

L55 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1990:32886 HCAPLUS
DOCUMENT NUMBER: 112:32886
TITLE: Studies on angiotensin-converting enzyme
inhibitors: protease catalyzed
resolution of aryl 3-mercapto-2-methylpropionic ester
AUTHOR(S): Chen, Shui Tein; **Wong, Chi Huey**
CORPORATE SOURCE: Inst. Biochem. Sci., Natl. Taiwan Univ. Taipei
Taiwan
SOURCE: Journal of the Chinese Chemical Soc.
Taiwan) (1989), 36(5), 451-8
CODEN: JCCTAC; ISSN: 0009-4536
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Optically active 3-benzylthio-2-methylpropionic acid and 3-benzoylthio-2-methylpropionic acid have been prepared and catalyzed hydrolysis of their corresponding ester and Subtilisin catalyzed the hydrolysis of the thioester of 3-benzoylthio-2-methylpropionate twice as fast as that of the Me ester derivative. The stability of the enzyme in organic cosolvents was studied. Immobilization of subtilisin on the solid support XAD-8 improved the stability of the enzyme. A practical preparative resolution of the title compound is reported.

L55 ANSWER 5 OF 8 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1995:55289 BIOSIS
DOCUMENT NUMBER: PREV199598069589
TITLE: Recombinant aprotinin in coronary artery bypass graft surgery.
AUTHOR(S): Green, D. [Reprint author]; Sanders, J. [Reprint author]; Eiken, M.; **Wong, C. A.**; Frederiksen, J.; Jacob A.; Palmer, A.; Trowbridge, A.; Tabanera, R.; Edsberg, B.
CORPORATE SOURCE: Dep. Med., Univ. Chicago, Chicago, IL
SOURCE: Blood, (1994) Vol. 84, No. 10 S
Meeting Info.: Abstracts Submit
Meeting of the American Society
Tennessee, USA. December 2-6, 1994
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jan 1995
Last Updated on STN: 1 Feb 1995

L55 ANSWER 6 OF 8 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1988:500184 BIOSIS
DOCUMENT NUMBER: PREV198886120868; BA86:120868
TITLE: ENZYMES IN CARBOHYDRATE SYNTHESIS N ACETYLNEURAMINIC ACID

ALDOLASE CATALYZED REACTIONS AND PREPARATION OF N
ACETYL-2-DEOXY-D-NEURAMINIC ACID DERIVATIVES.
AUTHOR(S): KIM M-J [Reprint author]; HENNEN W J; SWEERS H M; **WONG**
C-H
CORPORATE SOURCE: DEP CHEM, TEX A AND M UNIV, COLLEGE STATION, TEX 77843, USA
SOURCE: Journal of the American Chemical Society, (1988) Vol. 110,
No. 19, pp. 6481-6486.
CODEN: JACSAT. ISSN: 0002-7863.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 22 Nov 1988
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AB This paper describes the structural characteristics of substrates accepted by N-acetylneuraminic acid (Neu5Ac) aldolase (E.C. 4.1.3.3), the results from its stability studies, its use in the synthesis of Neu5Ac and 9-O-acetyl-Neu5Ac (Neu5,9Ac2), and the chemical conversion of Neu5Ac to the 2-deoxy derivatives. Values of kinetic parameters (K_m and V_{max}) for 14 aldoses including N-acetyl-D-mannosamine (ManNAc) and pyruvate were determined at pH 7.5 and 25° C in the direction of condensation. The 30.sbd.50-mmol-scale synthesis using ManNAc, excess pyruvate, and PAN-immobilized Neu5Ac aldolase provided multigram quantities of Neu5Ac (yield, 87-91% in solution and 67% in isolated products) without a significant loss of enzyme activity. The synthesis using two separate enzyme reactions, acetylation of ManNAc to 6-O-acetylManNAc to 6-O-acetylManNAc catalyzed by **protease N** and condensation of 6-O-acetyl-ManNAc with pyruvate catalyzed by Neu5Ac aldolase, provided Neu5,9Ac2 in 59% overall yield. To illustrate the utility of Neu5Ac as a synthetic starting material, a potential **inhibitor** of Neu5Ac-associated enzymes was prepared. Three chemical steps from Neu5Ac provided methyl 4,7,8,9-tetra-O-acetyl-N-acetyl-2-deoxy- α -neuraminic acid (2-deoxy- α -Neu4,5,7,8,9Ac5OMe) in 50% overall yield. Its structure was analyzed by ¹H and ¹³C NMR spectroscopy and X-ray crystallography.

L55 ANSWER 7 OF 8 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1986:399099 BIOSIS
DOCUMENT NUMBER: PREV198682084579; BA82:84579
TITLE: SELECTIVE INHIBITION OF PROTEOLYTIC ENZYMES IN AN IN-VIVO
MOUSE MODEL FOR EXPERIMENTAL METASTASIS.
AUTHOR(S): OSTROWSKI L E [Reprint author]; AHSAN A; SUTHAR B P; PAGAST
P; BAIN D L; **WONG C**; PATEL A; SCHULTZ R M
CORPORATE SOURCE: DEP BIOCHEMISTRY AND BIOPHYSICS, STRITCH SCH MED, LOYOLA
UNIV CHICAGO, MAYWOOD, ILLINOIS 60153, USA
SOURCE: Cancer Research, (1986) Vol. 46, No. 8, pp. 4121-4128.
CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 4 Oct 1986
Last Updated on STN: 4 Oct 1986

AB Peptide aldehyde transition state analogue **inhibitors** of serine and cysteine **proteases** have been used to selectively **inhibit proteases** for which prior evidence supports a role in tumor cell metastasis. These enzymes include cathepsin B, urokinase plasminogen activator (PA), and thrombin. The **inhibition** constants of the peptidyl aldehyde **inhibitors** show that they are highly selective for a particular targeted serine or cysteine **protease**. The **inhibitors** are introduced by i.p. injection or by miniosmotic pumps into syngeneic C57BL/6 mice also

given injections of B16-F10 melanoma cells, and the number of metastatic foci in the lung was determined. While the injection protocol gave an initially high but changing in vivo concentration of **inhibitor** over time, the minipump implant gave a constant steady state concentration of **inhibitor** over 5-7 days. Minipump infusion of leupeptin (acetyl-leucylleucylargininal), a strong **inhibitor** of cathepsin B at a steady state plasma concentration 1000-fold greater than its K_i (cathepsin B), gave no significant decrease in lung colonization by the B16 tumor cells. Ep475, a stoichiometric irreversible peptide **inhibitor** of cathepsin B-like **proteases**, also did not significantly **inhibit** metastatic foci formation. Introduction of selective **inhibitors** of urokinase PA, tert-butylloxycarbonylglutamylglycylargininal and H-glutamylglycylargininal at concentrations near its K_i , produced no significant decrease in mouse lung colonization. The selective thrombin **inhibitor** D-phenylalanylprolylargininal infused to a steady state concentration 100-fold greater than its K_i dramatically increased B16 melanoma colonization of mouse lung. The results indicate that neither secreted cathepsin B-like nor urokinase PA have roles in B16 colonization of mouse lung, while thrombin may have a role in preventing metastasis. These experiments do not eliminate roles for a cathepsin B-like enzyme or urokinase PA in the initial steps of the metastatic process.

L55 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 ACCESSION NUMBER: 1979:241357 BIOSIS
 DOCUMENT NUMBER: PREV197968043861; BA68:43861
 TITLE: STRUCTURE OF ACID **PROTEASE** FROM
 ENDOTHIA-PARASITICA IN CROSS LINKED FORM AT 2.45 ANGSTROM
 RESOLUTION.

AUTHOR(S): **WONG C-H** [Reprint author]; LEE T J; LEE T-Y; LU
 T-H; YANG I-H

CORPORATE SOURCE: NATL TSING HUA UNIV, HSINCHU, TAIWAN, CHINA
 SOURCE: Biochemistry, (1979) Vol. 18, No. 8, pp. 1638-1640.
 CODEN: BICHAW. ISSN: 0006-2960.

DOCUMENT TYPE: Article

FILE SEGMENT: BA

LANGUAGE: ENGLISH

AB The structure of acid **protease** from *E. parasitica* in strongly cross-linked form is compared with that of the untreated protein at 2.45 Å resolution. The only observed conformation change introduced by the cross-linking reaction is at the N terminal. The 2 main chain structures are essentially identical. Approximately 2 molecules of the **inhibitor**, 1,2-epoxy-3-(p-nitrophenoxy)propane, are incorporated into each protein molecule. They are covalently bound to the 2 aspartic residues at the active center.

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 L24: Parent set
 L31: Refined structure
 L33: Refined set
 L35: Remove sequences
 L37: Str. where $R_1=R_2=R_3=H$
 L40: set where "
 L41: Remove hits where
 $R_1=R_2=R_3=H$ (cl. 19 line
 30 proviso)

09/077,712 ②
 L42: STR where $R_2=OBn$
 (unsubstituted)
 L44: set where $R_2=OBn$
 L45: Remove hits where
 $R_2=OBn$

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